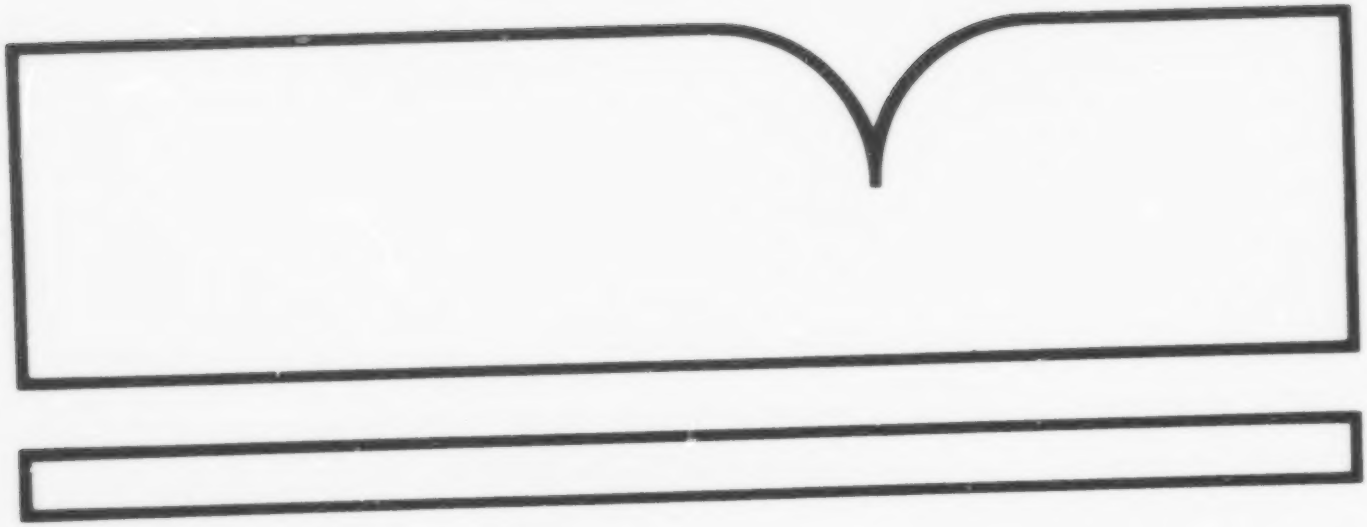
PB88-137757

Health and Environmental Effects Profile for Bromobenzenes

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA-600/X-84-128	2.	3. RECIPIENT'S ACCESSION NO. PB88 137757/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Bromobenzenes		5. REPORT DATE January 1984
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for Bromobenzenes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Bromobenzenes as a class.

1,4-Dibromobenzene, 1,2,4-Tribromobenzene and Hexabromobenzene have been determined to be systemic toxicants. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 1,4-Dibromobenzene is 1×10^{-2} (mg/kg bw/day), for 1,2,4-Tribromobenzene is 5×10^{-3} (mg/kg bw/day) and for Hexabromobenzene is 2×10^{-3} (mg/kg bw/day) for oral exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 62
	20. SECURITY CLASS (This page) Unclassified	22. PRICE PC 12.95 / MF 6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-137757

EPA/600/X-84/128
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR BROMOBENZENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
	1.1. STRUCTURE CAS NUMBER	1
	1.2. PHYSICAL AND CHEMICAL PROPERTIES	2
	1.3. PRODUCTION DATA	5
	1.4. USE DATA	7
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	8
	2.1. AIR	8
	2.2. WATER	9
	2.3. SOIL	12
3.	EXPOSURE	14
	3.1. WATER	14
	3.2. FOOD	14
	3.3. AIR	14
	3.4. DERMAL	15
4.	PHARMACOKINETICS	16
	4.1. ABSORPTION	16
	4.2. DISTRIBUTION	16
	4.3. METABOLISM	17
	4.4. EXCRETION	19
5.	EFFECTS	22
	5.1. CARCINOGENICITY	22
	5.2. MUTAGENICITY	22
	5.3. TERATOGENICITY	24
	5.4. OTHER REPRODUCTIVE EFFECTS	25
	5.5. CHRONIC TOXICITY	25
	5.6. OTHER RELEVANT INFORMATION	28
6.	AQUATIC TOXICITY	32
	6.1. ACUTE TOXICITY	32
	6.2. CHRONIC TOXICITY	32
	6.3. PLANT EFFECTS	32
	6.4. RESIDUES	32

Page

7. EXISTING GUIDELINES AND STANDARDS 34

7.1. HUMAN. 34
7.2. AQUATIC. 34

8. RISK ASSESSMENT 35

9. REFERENCES. 38

APPENDIX: LITERATURE SEARCHED 51

LIST OF TABLES

Table		Page
1-1	Production Data for Bromobenzenes	6
4-1	Urinary and Fecal Metabolites of Brominated Benzenes.	20
5-1	Mutagenicity of Bromobenzene.	23

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
i.v.	Intravenous
LC_{50}	Concentration lethal to 50% of recipients
LD_{85}	Dose lethal to 85% of recipients
LT_{50}	Time lethal to 50% of recipients
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
p.o.	Per os
ppm	Parts per million
ppt	Part per trillion
UV	Ultraviolet
w/v	Weight per volume

1. INTRODUCTION

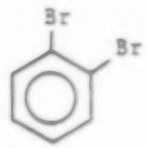
1.1. STRUCTURE AND CAS NUMBER

Nine brominated benzenes are the subject of this hazard profile. The structure, molecular formula, molecular weight, Chemical Abstracts Service (CAS) Registry Number and common synonyms for the subject chemicals are summarized below:

Bromobenzene

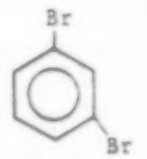
Molecular formula: C_6H_5Br
Molecular weight: 157.02
CAS Number: 108-86-1
Synonyms: monobromobenzene
phenyl bromide
benzene, monobromo-

1,2-Dibromobenzene



Molecular formula: $C_6H_4Br_2$
Molecular weight: 235.92
CAS Number: 583-53-9
Synonyms: o-dibromobenzene
benzene, 1,2-dibromo-

1,3-Dibromobenzene



Molecular formula: $C_6H_4Br_2$
Molecular weight: 235.92
CAS Number: 108-36-1
Synonyms: m-dibromobenzene
benzene, 1,3-dibromo-

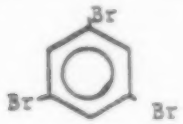
1,4-Dibromobenzene

Molecular formula: $C_6H_4Br_2$
Molecular weight: 235.92
CAS Number: 106-37-6
Synonyms: p-dibromobenzene
p-bromophenyl bromide
benzene, 1,4-dibromo-

Dibromobenzene

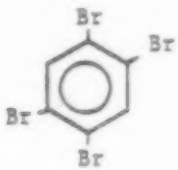
Molecular formula: $C_6H_4Br_2$
Molecular weight: 235.92
CAS Number: 26249-12-7
Synonym: benzene, dibromo-

1,3,5-Tribromobenzene



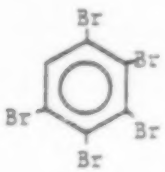
Molecular formula: $C_6H_3Br_3$
Molecular weight: 314.82
CAS Number: 626-39-1
Synonym: benzene, 1,2,5-tribromo-

1,2,4,5-Tetrabromobenzene



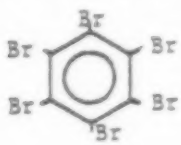
Molecular formula: $C_6H_2Br_4$
Molecular weight: 393.72
CAS Number: 636-28-2
Synonym: benzene, 1,2,4,5-tetrabromo- 2,3,5,6-tetrabromobenzene

Pentabromobenzene



Molecular formula: C_6HBr_5
Molecular weight: 472.62
CAS Number: 608-90-2
Synonym: benzene, pentabromo-

Hexabromobenzene



Molecular formula: C_6Br_6
Molecular weight: 551.52
CAS Number: 87-82-1
Synonym: benzene, hexabromo-

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Information on the physical and chemical properties of the subject bromobenzenes was obtained, except as noted, from Windholz (1976) and Weast (1980).

Bromobenzene

Description:	mobile liquid with aromatic odor
Melting Point:	-30.6°C
Boiling Point:	156.2°C
Density:	$d_{1.4952}^{20}$
Vapor Pressure (25°C):	4.1 mm Hg (Mackay et al., 1980)
Water Solubility (25°C):	359.7 mg/ℓ (Yalkowsky et al., 1979)
Log Octanol/Water Partition Coefficient (observed):	2.99 (Swann et al., 1980) 3.01 (Wataral et al., 1982)

1,2-Dibromobenzene

Description:	not available
Melting Point:	7.1°C
Boiling Point:	225°C
Density:	d_0^4 1.9843
Water Solubility (25°C):	74.6 mg/ℓ (Yalkowsky et al., 1979)
Log Octanol/Water Partition Coefficient:	3.64 (Hansch and Leo, 1979)

1,3-Dibromobenzene

Description:	not available
Melting Point:	-7°C
Boiling Point:	218°C
Density:	d_0^4 1.9523
Vapor Pressure (25°C):	0.43 mm Hg (Mackay et al., 1980)
Water Solubility (25°C):	98.3 mg/ℓ (Yalkowsky et al., 1979)
Log Octanol/Water Partition Coefficient:	3.75 (Hansch and Leo, 1979)

1,4-Dibromobenzene (p-Dibromobenzene)

Description:	not available
Melting Point:	87.3°C
Boiling Point:	218-219°C
Density:	1.5742
Vapor Pressure (25°C):	0.24 mm Hg (Mackay et al., 1980)
Water Solubility (25°C):	20.1 mg/ℓ (Yalkowksy et al., 1979)
Log Octanol/Water Partition Coefficient (observed):	3.79 (Wataral et al., 1982)

Dibromobenzene

Description:	not available
Melting Point:	not available
Boiling Point:	not available
Density:	not available
Water Solubility:	not available
Log Octanol/Water Partition Coefficient:	not available

1,3,5-Tribromobenzene

Description:	needles or prisms
Melting Point:	87.8°C
Boiling Point:	not available
Density:	2.658
Water Solubility (25°C):	1.37 mg/ℓ (Yalkowsky et al., 1979)
Log Octanol/Water Partition Coefficient (observed):	4.51 (Wataral et al., 1982)

1,2,4,5-Tetrabromobenzene

Description:	monoclinic prisms
Melting Point:	182°C
Boiling Point:	not available
Density:	d_0^4 3.072

Water Solubility (25°C):	41.2 µg/ℓ (Yalkowsky et al., 1979)
Log Octanol/Water Partition Coefficient (observed):	5.13 (Wataral et al., 1982)

Pentabromobenzene

Description:	white needles
Melting Point:	160-161°C
Boiling Point:	sublimes
Density:	not available
Water Solubility:	not available
Log Octanol/Water Partition Coefficient:	not available

Hexabromobenzene

Description:	monoclinic needles
Melting Point:	not available
Boiling Point:	327°C
Density:	not available
Water Solubility:	not available
Log Octanol/Water Partition Coefficient:	not available

1.3. PRODUCTION DATA

Brominated benzenes can be synthesized by the reaction of bromine with hot benzene in the presence of ferric halide. Disubstitution products (mainly 1,4-dibromobenzene) are, however, the major brominated benzenes formed by this method (Purcell, 1979).

Current production of brominated benzenes is likely to be <10,000 pounds/year (SRI, 1983; U.S. EPA, 1977) and is summarized in Table 1-1.

TABLE 1-1

Production Data for Bromobenzenes*

Chemical	Producer	Quantity (pounds/year)
Bromobenzene	Dow Chemical Co. Midland, MI	None
	Great Lakes Chemical Co. El Dorado, AR	NR
1,2-Dibromobenzene	Kodak Rochester, NY	None
1,3-Dibromobenzene	Kodak Rochester, NY	<1000
1,4-Dibromobenzene	Dow Chemical Co. Midland, MI	NR
Dibromobenzene	Dow Chemical Co. Midland, MI	None
	Great Lakes Chemical Co. El Dorado, AK	NR
1,3,5-Tribromobenzene	Kodak Rochester, NY	<1000
1,2,4,5-Tetrabromobenzene	Kodak Rochester, NY	<1000
Pentabromobenzene	NA	NA
Hexabromobenzene	Columbia Organic Chemical Co. Columbia, SC	<1000

*Source: SRI, 1983; U.S. EPA, 1977

NR = Not reported

NA = Not available

1.4. USE DATA

Information on the use of brominated benzenes is limited to bromobenzene, 1,2-dibromobenzene and 1,4-bromobenzene (Ringk and Theimer, 1979; Stenger, 1979; Griffin, 1979) and hexabromobenzene (Larson, 1979). Bromobenzene is used as an emulsifier of fats and oils (Griffin, 1979) and in the Grignard reaction with formaldehyde to form benzyl alcohol (Ringk and Theimer, 1979). The 1,2-dibromobenzene is used as a dense liquid for solid separation based on differences in specific gravity, as an ingredient in heat-transfer media or transformer oils, and as a solvent for waxes, fats, and resins. Both 1,2- and 1,4-dibromobenzene are used as intermediates in organic synthesis (Stenger, 1979). Hexabromobenzene is used as a flame retardant additive in plastics (Larson, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Little specific information is available regarding the environmental transport and fate of the brominated benzenes, possibly because production and usage are not widespread. Extensive data are available on structurally analogous chlorobenzenes, and these data can be used to predict environmental behavior.

2.1. AIR

It appears that the lower brominated benzenes can photolyze via homolysis of the carbon-bromine bond (Grimshaw and de Silva, 1981). Nojima et al. (1980) reported, for example, 37% degradation of bromobenzene (~1 ppm) in air to phenol and 4-bromophenol after irradiation for 5 hours by a xenon lamp in a quartz vessel at 25-30°C. Similar irradiation of ~1 ppm bromobenzene in the presence of ~1 ppm nitric oxide in air yielded 87% degradation; the major products observed were phenol, 4-nitrophenol, 2,4-dinitrophenol, 4-bromophenol, 3-bromo-4-nitro-phenol, 2-bromo-4-nitrophenol and 2,6-dibromo-4-nitrophenol.

Experimental studies with chlorinated benzenes suggest that the brominated benzenes are susceptible to attack by hydroxyl radicals in the air (Ware and West, 1977; U.S. EPA, 1983a). Half-life estimates of several days have been reported for reaction of OH• with the dichlorobenzenes, 1,2,4-trichlorobenzene and hexachlorobenzene (Brown et al., 1975; Simmons et al., 1976). 2- and 4-Dichlorobenzene and hexachlorobenzene reportedly are resistant to auto-oxidation by ozone in the air (Brown et al., 1975).

Singh et al. (1981) monitored the atmospheric concentrations of several chlorinated benzenes in California and Arizona over 2-week periods and made estimates of residence times. The estimated atmospheric residence times and

daily loss rates for monochlorobenzene, the dichlorobenzenes and an unspecified isomer of trichlorobenzene were reported to be 13 days and 7.4%, 38.6 days and 2.6%, and 116 days and 0.9%, respectively.

As discussed in Sections 2.2. and 2.3., the lower brominated benzenes are likely to enter the atmosphere as a result of volatilization from water and soil. The moderately high octanol water partition coefficients and low water solubilities suggest that the brominated benzenes, particularly the higher brominated benzenes, will exist in the atmosphere in the particulate sorbed phase, and that dry deposition is likely to be the predominate removal mechanism.

2.2. WATER

The chemical and photolytic degradation of the brominated benzenes in water has not been experimentally investigated. There is a possibility that mono- and polyhydric phenols could be produced through hydrolysis, but the rate would be very slow because of the insolubility of the compounds (Ware and West, 1977). The polybrominated benzenes would be attacked more easily by nucleophiles such as OH^- than the lower brominated benzenes because of the electron withdrawing effect of the added bromines. The brominated benzenes should be resistant to auto-oxidation by peroxyradicals in water since 2-dichlorobenzene, 4-dichlorobenzene and hexachlorobenzene reportedly do not react with $\cdot RO_2$ (Brown et al., 1975).

Studies in air (Nojima et al., 1980) suggest that photocatalyzed debromination could occur in water. Irradiation of monobromobenzene in isopropanol (~6 g/ℓ) for 6 hours with a 125-W medium pressure mercury arc lamp in a water-cooled quartz well yielded 72% benzene (Pinhey and Rigby, 1969).

Exposure of 1,4-dichlorobenzene to UV in aqueous solutions with various suspended sediments did not result in degradation, possibly due to a light-shielding effect of the sediments (Oliver et al., 1979; Ware and West, 1977). Hexachlorobenzene in aqueous solution has been shown to be photochemically stable (U.S. EPA, 1983a).

Limited data indicate that the lower brominated benzenes may be degraded by microorganisms in water. Gibson et al. (1968) found that Pseudomonas putida was capable of oxidizing bromobenzene to 3-bromocatechol. In this study cultures of P. putida were exposed to toluene vapor for 15 hours and monobromobenzene vapor was added as an additional substrate for a further 10 hours; monobromobenzene did not serve as a growth substrate when introduced into the medium alone. Shelat and Patel (1973) reported that Bacillus polymyxa, isolated from sewage sludge, used a mineral solution containing 0.5% w/v monobromobenzene as the sole source of carbon. Growth was indicated by colony formation after 72 hours of incubation at 28°C, but the method of utilization was not determined. Sasaki (1978) concluded that hexabromobenzene is "almost not biodegradable." Biodegradation of hexabromobenzene and ~300 other chemicals was evaluated by measurement of oxygen uptake of active sludge (MITI BOD protocol); if biodegradation exceeded 30% after 2 weeks of incubation at 25°C, the test substance was usually considered to be "well-biodegradable."

A number of studies examined the biodegradability of the chlorinated benzenes (Ware and West, 1977; U.S. EPA, 1983a), and these data also indicate that biodegradability decreases as the number of halogen substituents increases. Many of the studies of chlorinated benzenes used sewage or treatment plant microorganisms, presented BOD data that were quite variable

with respect to extent of degradation, did not determine rates of degradation, and/or apparently did not quantify the likely significant role of evaporation. Chemical monitoring of substrate concentration of 1,2-dichlorobenzene (Davis et al., 1981) and 1,2,4-trichlorobenzene (Simmons et al., 1976) suggest that the lower chlorinated benzenes may be degraded in water containing industrial or municipal treatment plant microbes within 7-14 days. The presence of lower brominated benzenes in ambient water (Chapter 3), however, indicates that degradation of the brominated benzenes under typical environmental conditions may take significantly longer. Hexachlorobenzene reportedly showed no degradation by river water or sediment microbes (U.S. EPA, 1983a).

The brominated benzenes have low solubility in water, and the solubility decreases with increasing bromine substitution (see Section 1.2.). Data on rates of evaporation of the brominated benzenes are not available, but it is expected that they will, like the chlorinated benzenes, tend to evaporate quickly (the chlorinated benzenes have high activity coefficients in water) (U.S. EPA, 1983a). Laboratory and theoretical studies indicate that complete evaporation of the lower chlorinated benzenes from aqueous solutions can occur within a range of several hours to several days, and a field study of 1,4-dichlorobenzene in lake water has shown that transport into the atmosphere is the predominant mechanism of loss from the lake ($t_{1/2}$ ~100 days) (Schwarzenbach et al., 1979).

The low water solubilities and the relatively high octanol/water partition coefficients of the higher brominated benzenes (see Section 1.2.) suggest that they are likely to be associated with suspended particulate matter and bottom sediments. These properties also suggest that the higher brominated benzenes will bioaccumulate in aquatic organisms. The results of

numerous studies with chlorinated benzenes (Ware and West, 1977; U.S. EPA, 1983a) indicate that the BCFs of brominated benzenes should increase with increasing degree of bromine substitution. Two investigators have reported, however, that hexabromobenzene did not accumulate under static conditions in juvenile Atlantic salmon, Salmo salar, exposed to 42 ppm for 48 or 96 hours (Zitko and Hutzinger, 1976) or in carp, Cyprinus carpio, exposed to 1/100 the 48-hour LC_{50} (not stated) for up to 8 weeks (Sasaki, 1978). Both of these studies also showed that hexachlorobenzene accumulated in these fish when tested under similar conditions, indicating that the bioaccumulative properties of the chlorinated benzenes may not accurately predict bioaccumulation of the analogous brominated benzenes.

2.3. SOIL

The fate of the brominated benzenes in soil has not been investigated experimentally. Hydrolysis is not likely to occur to a significant extent in soil water (see Section 2.2.), but photocatalyzed degradation could occur at the surface (see Section 2.1.), particularly of the higher brominated benzenes, which probably remain strongly sorbed to soils. Degradation studies in water (see Section 2.2.) and studies with chlorinated benzenes suggest that some biological degradation of the lower bromobenzenes may occur in soil, and that the primary degradation products may be brominated phenols. The persistence of these compounds in soil is directly related to the degree of bromine substitution; soil half-lives are estimated to be on the order of weeks (lower brominated benzenes) to years (penta- and hexabromobenzene) (U.S. EPA, 1983a).

A measured soil sorption constant (K_{oc}) of 150 (Kenaga, 1980) and measured octanol/water partition coefficients of ~1000 (Swann et al., 1980;

Wataral et al., 1982) for monobromobenzene suggest that this compound is likely to be moderately mobile. Increasingly greater octanol/water partition coefficients and decreasing water solubilities for the higher brominated benzenes (see Section 1.2.) suggest that soil adsorption probably increases with increasing number of bromine substitutents. Laboratory and field studies with lower chlorinated benzenes (e.g., monochlorobenzene, 1,4-dichlorobenzene and 1,2,4-trichlorobenzene) further suggest that the lower brominated benzenes may be mobile enough to leach into groundwater, but hexachlorobenzene is immobile and not likely to leach, particularly in soils with high organic contents (U.S. EPA, 1983a). Other chlorinated benzenes data indicate that transport into the air or adjacent soil via vapor phase diffusion is likely to occur to a significant extent, particularly for the lower brominated benzenes and in dry, porous soils (U.S. EPA, 1983a).

3. EXPOSURE

3.1. WATER

There has been a low frequency of detection of brominated benzenes in surveys of organic compounds in water, but monobromobenzene has been detected at various sites throughout the United States, including the Delaware River basin, the Mississippi River, the Hudson River and Lake Michigan (U.S. EPA, 1983b; Ewing et al., 1977; Konasewich et al., 1978; DeWalle and Chian, 1978; Pellizzari et al., 1979). STORET contains 8 unremarked observations for monobromobenzene in stream water which were reported in 1976. The average concentration is 12.75 µg/ℓ, with a range of 3-38 µg/ℓ. Monobromobenzene has also been detected in secondary effluents from industrial plants (Ellis et al., 1982) and in sediment and soil in the vicinity of brominated benzene industrial facilities in El Dorado and Magnolia, Arkansas (DeCarlo, 1979). Monitoring data for the other brominated benzenes in water were not located in the available literature, but DeCarlo (1979) detected di-, tetra- and hexabromobenzene in sludge samples obtained from a PBB manufacturing facility discharge zone in Bayonne or Sayerville (not specified), NJ.

3.2. FOOD

Pertinent data regarding brominated benzenes in food could not be located in the available literature. The nature of use of the brominated benzenes suggests that contamination of food would be unlikely.

3.3. AIR

Monobromobenzene has been detected in the air of suburban areas in the vicinity of emission sources (Brodzinsky and Singh, 1982). The mean concentrations for samples taken during 1976-1978 in El Dorado, AR (35 data

points) and Magnolia, AR (28 data points) were 210 ppt (range, 0.83-2100 ppt) and 1.5 ppt (range, 0-8.3 ppt). Monobromobenzene was not detected in a limited number of air samples from the vicinity of Edison, NJ (1 data point) or in the Grand Canyon, AZ (7 data points).

3.4. DERMAL

Pertinent data regarding the dermal effects of brominated benzenes could not be located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Based on the available animal toxicity studies (Chapter 5), mono- and polybrominated benzenes, including hexabromobenzene, appear to be absorbed in the digestive tract. Quantitative data are not available and cannot be inferred. No data are available on the absorption of brominated benzenes by other natural routes.

4.2. DISTRIBUTION

The distribution of brominated benzenes following their administration by natural routes has not been studied extensively. Following oral administration, bromobenzene (Siegers, 1978), 1,2,4-tribromobenzene (Carlson, 1978), and hexabromobenzene (Mendoza et al., 1979; Smith and Francis, 1980) appear to be distributed to the liver, where metabolism occurs, with accumulation of hexabromobenzene in the adipose tissue (Mendoza et al., 1977). Male rats fed 0, 10, 20, 40, 80 or 160 ppm hexabromobenzene in the diet for 12 weeks, and killed after being fasted overnight, had a dose-dependent accumulation of hexabromobenzene in their adipose tissue (Mendoza et al., 1977). At dietary levels <40 ppm, residues in adipose tissue were below the detection limit of 0.1 ppm, but at higher dietary levels (i.e., 80 and 160 ppm), hexabromobenzene concentrations in adipose tissue increased by about 3-fold for every 2-fold increase in dietary concentration. At the 160 ppm dietary level, the concentration of hexabromobenzene in adipose tissue was 55 ppm, 28 times higher than the concentration in the liver; concentrations in other tissues, including the kidneys, were less than the concentration in the liver.

When administered by i.p. or i.v. injection, bromobenzene has been detected in the liver, kidneys, small intestines, lungs and adipose tissue (Monks et al., 1982a; Zampaglione et al., 1973) soon after administration.

Following a single i.p. dose of bromobenzene (750 mg/kg) in male Sprague-Dawley rats, Reid et al. (1971a) reported that a major portion of the dose was distributed in the fat (5600 µg/g tissue) within 4 hours, while lesser amounts occurred in the liver (282 µg/g), kidney (235 µg/g) and other tissues. Plasma levels were reported at 34 µg/g at 4 hours. Tissue and plasma levels gradually decreased as bromobenzene was metabolized and excreted. Jollow et al. (1974) reported that bromobenzene persisted for >24 hours after i.p. administration due to its slow absorption from the peritoneal cavity as compared to i.v. injection. Whether administered by natural or non-natural routes, brominated benzenes appear to accumulate in adipose tissue until metabolized in the liver and excreted.

4.3. METABOLISM

An abundance of data regarding the metabolism of brominated benzenes is made available through investigations into the mechanism of hepatotoxicity of these compounds. Bromobenzene is oxidized by hepatic mixed-function oxidase systems requiring cytochrome P-450 or P-448, NADH and NADPH, to form epoxide intermediates, bromobenzene 2,3- and 3,4-epoxides (Thor et al., 1978a; Hesse et al., 1982). These intermediate epoxides are presumed to be the cytotoxic agents, with the 3,4-epoxide being more reactive and binding more extensively to microsomal and cellular proteins (Lau and Zannoni, 1979, 1981a). The oxidation of bromobenzene to o-bromophenol, proceeding through the bromobenzene 2,3-epoxide intermediate (Monks et al., 1982b), required cytochrome P-448 LM_4, in the rabbit (Lau and Zannoni, 1981b). The oxidation of bromobenzene to p-bromophenol via the 3,4-epoxide was catalyzed by hepatic cytochrome P-450 LM_2 (LM stands for liver microsomes, while 2 and 4 refer to the phenobarbital and 5,6-benzoflavone-inducible form, respectively). Selective pretreatment of animals with phenobarbital, which can

increase cytochrome P-450 activity 16-fold (45.6 nmole p-bromophenol produced/min/100 mg uninduced microsomal protein; 735.0 nmole p-bromophenol/min/100 mg phenobarbital pretreated microsomal protein) enhances the formation of bromobenzene 3,4-epoxide (Lau and Zannoni, 1979). The accelerated formation of this toxic intermediate enhances the cytotoxic/cytolethal effect of bromobenzene. Pretreatment with inducers of cytochrome P-448, such as ß-naphthoflavone or 3-methylcholanthrene, preferentially enhances metabolism of bromobenzene to the 2,3-epoxide isomer and causes a marked reduction in hepatocellular toxicity as compared with hepatotoxicity in uninduced rats (Reid et al., 1971b; Lau and Zannoni, 1979). Billings et al. (1982) reported that bromobenzene was oxidized to many metabolites by phenobarbital-pretreated rat hepatocytes, 2-, 3- and 4-hydroxybromobenzene, 2,3- and 3,4-dihydroxybromobenzene, 4-bromocatechol and o-methyl, 4-bromocatechol.

Following the oxidation of bromobenzene, formed metabolites are conjugated to hepatic gluthathione, thereby reducing the cytotoxic effect (Thor et al., 1979). Hepatic glutathione levels can be rapidly depleted after bromobenzene treatment, which results in increased hepatocellular damage (Thor et al., 1978b). Glutathione levels can be maintained by stimulating its resynthesis, or by methionine, cysteine or N-acetyl cysterine, in isolated hepatocytes (Thor et al., 1978a, 1979, 1982). Thus, the presence of glutathione and its resynthesis is an important element in the elimination of toxic metabolites of bromobenzene, minimizing cytotoxicity. Zampaglione et al. (1973) and Jollow et al. (1974) reported that in rats, as the dose of bromobenzene increased, glutathione levels were further depleted, more bromobenzene 3,4-epoxide accumulated, causing more cellular damage, and more 4-bromophenol was excreted as the final metabolite.

4.4. EXCRETION

In male Sprague-Dawley rats, the urinary metabolites of a non-toxic dose of bromobenzene (0.05 mmole/kg, administered intravenously) were bromophenyl mercapturic acid (70% of total urinary metabolites), 4-bromophenol (18%), bromocatechol (4%), bromophenyl-dihydrodiol (4%) and 2-bromophenol (3%) (Zampaglione et al., 1973). The same metabolites after a toxic dose (10.0 mmole bromobenzene/kg, administered intraperitoneally) accounted for 48, 37, 6, 4 and 4%, respectively, of the total urinary metabolites. Urinary metabolites accounted for >90% of the administered bromobenzene at both dose levels. An increase in the percentage of 4-bromophenol, seen concurrently with cytotoxic doses of bromobenzene, is consistent with the theory that bromobenzene 3,4-epoxide (which is ultimately oxidized to 4-bromophenol) is the cytotoxic agent (Zampaglione et al., 1973). Lertratanangkoon et al. (1982) reported mercapturic, mercaptoacetic, mercaptolactic and methylthio-conjugates of bromobenzene metabolites found in rat and guinea pig urine. Evidence from this study indicates that some diepoxidation occurs during bromobenzene metabolism. Both p- and m-bromophenol and p-bromophenylmercapturic acid were identified in urine of rats and rabbits dosed orally with bromobenzene (Gillham and Young, 1968). Ruzo et al. (1976) studied the urinary and fecal metabolites of several brominated benzenes administered to rabbits by i.p. injection at ~50 mg/kg (Table 4-1). Oxidation to phenolic derivatives was the primary metabolic pathway, and bromine migration was evident, suggesting that epoxide intermediates were formed. The urinary and fecal metabolites of hexabromobenzene (16.6 mg/kg), administered orally to female Wistar rats every other day for 2 weeks, were reported by Koss et al. (1982). Fecal and urinary metabolites included unchanged hexabromobenzene,

TABLE 4-1

Urinary and Fecal Metabolites of Brominated Benzenes[a]

Administered Compound (50 mg/kg)	Urinary and/or Fecal Metabolite
Bromobenzene	4-bromophenol 3-bromophenol
1,2-Dibromobenzene	2,3-dibromophenol 3,4-dibromophenol
1,3-Dibromobenzene	2,4-dibromophenol[b] 2,6-dibromophenol[b]
1,4-Dibromobenzene	2,4-dibromophenol 2,5-dibromophenol
1,3,5-Tribromobenzene	2,4,6-tribromophenol 2,3,5-tribromophenol
1,2,4-Tribromobenzene	2,4,5-tribromophenol 2,4,6-tribromophenol
1,2,4,5-Tetrabromobenzene	c/
Pentabromobenzene	c/, d/

[a]Source: Ruzo et al., 1976

[b]Not positively identified by comparison with pure compound

[c]Yield of metabolites was minimal

[d]Trace (<0.01 mg) of pentabromophenol detected

pentabromoanisol, pentabromobenzene, a dimethoxy tetrabromobenzene, pentabromothioanisol, tetrabromothioanisol and tetrabromodithioanisol. Of the administered dose ~20% was excreted as unchanged hexabromobenzene. The excretion of metabolites was predominantly in the feces, since urinary levels were very low (Koss et al., 1982).

Biliary metabolites of bromobenzene appear to be conjugates with glutathione. Sipes et al. (1974) reported that these conjugates are formed with bromobenzene 3,4-epoxide. Monks et al. (1982c) reported two glutathione conjugates [trans-3- and trans-4-bromo-6-(glutathione-S-yl)-cyclohexa-2,4-dien-1-ol], both formed from the 3,4-epoxide of bromobenzene and excreted in the bile. Sipes et al. (1974) reported that 5.6% of the intravenously administered ^{14}C-bromobenzene (20 mg/kg) had been excreted in the bile of rats within 3 hours and 24% had been excreted in the urine. A majority of the biliary metabolites must be reabsorbed from the intestine since, in rats, fecal excretion is minimal and urinary excretion accounts for ~90% of the administered dose (Zampaglione et al., 1973; Reid et al., 1971a).

5. EFFECTS

5.1. CARCINOGENICITY

Although bromobenzene is listed as a tumorigen by RTECS, no data to substantiate this point were presented by NIOSH (1983) or found in the available literature. Bromobenzene has recently been nominated for testing in a carcinogenesis bioassay by the National Toxicology Program (NTP, 1983).

No additional information regarding the carcinogenicity of brominated benzenes was available.

5.2. MUTAGENICITY

Bromobenzene was reported to have marginally positive activity in an assay with DNA repair deficient strains of E. coli (Rosenkranz and Poirier, 1979). The tests were performed either by placing 10 µl of the compound on filter discs and comparing the zone of inhibition between repair deficient (Poly A^-) and repair competent (Poly A^+) strains, or comparing survival of these strains following incubation with the compound (250 µg/ml) and bacteria in liquid media for 1 hour (Table 5-1). The response after application to filter discs was negative, while the response after exposure in liquid media was at the level designated to differentiate between a mutagenic and nonmutagenic response. Bromobenzene was nonmutagenic in TA1535 and TA1538 strains of Salmonella typhimurium when applied in the presence or absence of a microsomal activation system (rat liver derived). Incorporation of 10 µl of bromobenzene/plate resulted in no increase in mutants/plate when compared to control cultures (Rosenkranz and Poirier, 1979). In a host-mediated assay, strains TA1530 and TA1538 of S. typhimurium were exposed to bromobenzene in mice given 600 mg bromobenzene/kg bw (Simmon et al., 1979). There was no increase in the mutation frequency associated with bromobenzene treatment compared to spontaneous rates.

TABLE 5-1

Mutagenicity of Bromobenzene

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation (base-substitution)	S. typhimurium TA1535	plate incorporation	10 µl/plate	±	-	No increase in the number of revertants/plate was noted between exposed and control plates.	Rosenkranz and Poirier, 1979
Reverse mutation (frame-shift)	S. typhimurium TA1538	plate incorporation	10 µl/plate	±	-	No increase in the number of revertants/plate was noted between exposed and control plates.	Rosenkranz and Poirier, 1979
Growth inhibition	E. coli pol A^-/A^+	disc application	10 µl/plate	±	±*	Zone of inhibition for Poly A^- and Poly A^+ was 13.8 mm and 15.0 mm, respectively.	Rosenkranz and Poirier, 1979
DNA-modifying activity	E. coli pol A^-/pol A^+	liquid media incorporation	250 µg/ml	-	±*	Marginally positive preferential killing of pol A^- strain with survival index of 0.85.	Rosenkranz and Poirier, 1979
Sex chromosome nondisjunction	Drosphila	diet incorporation	1000 ppm	NA	-	No abnormal sex chromosome numbers were detected among $26x10^4$ flies.	Ramel and Magnusson, 1979
Reverse mutation	S. typhimurium TA1530, TA1538	host mediated (mice)	600 or 1000 mg/kg	+	-	Mutation frequency was neither different from nor less than control values.	Simmon et al., 1979
Mitotic recombination	Saccharomyces cerevisiae-D3	liquid media	0.1 µl/ml	±	-	Mitotic recombinants were not different from control values.	Simmon et al., 1979

*Marginally positive results

NA = Not Applicable

0474n

01/23/84

In an assay for mitotic recombinations in Saccharomyces cerevisiae D3, bromobenzene in liquid media (0.1 µl/ml) produced no increase in mitotic recombinants (Simmon, 1979). Bromobenzene (1000 ppm in the diet), tested in Drosophila, did not cause a significant increase in the frequency of sex chromosome-nondisjunction or loss of sex chromosomes among 26×10^3 flies (Ramel and Magnusson, 1979).

Data on the mutagenic activity of other brominated benzenes were not identified in the available literature.

5.3. TERATOGENICITY

The teratogenic effects of hexabromobenzene following its oral administration at 0, 50, 100 or 200 mg/kg on days 6-15 of gestation were examined in the litters of 20 Wistar rats (Khera and Villeneuve, 1975). Pregnant females were weighed to assess maternal toxicity. On day 22 of gestation, pregnant females were sacrificed and examined for visceral and uterine pathologies. Resorptions and fetal deaths were recorded. Fetuses were removed, weighed and examined for external malformations and viability. Viable fetuses were examined for skeletal terata and visceral anomalies. The incidence of skeletal or visceral defects was not significantly altered in fetuses exposed to hexabromobenzene when compared to vehicle controls. Sternal defects were noted in 5/103 and 5/99 fetuses from dams exposed at 100 and 200 mg/kg, while 0/92 and 1/93 were reported in the 50 mg/kg and control groups, respectively. The incidences of sternal defects in treated groups were not, however, statistically significantly different from the control incidence. Fetal deaths, fetal weight, numbers of live fetuses and maternal weights were not different between treated groups and vehicle control groups (Khera and Villeneuve, 1975).

A significant ($p<0.05$) increase in liver weight/body weight was observed in Wistar rat pups nursed by dams fed dietary hexabromobenzene (80 ppm for 101 days) when compared to unexposed pups (Mendoza et al., 1978). This difference was significant at 17 days but not at 21 days of age. By exposing pups during gestation, lactation, or both, Mendoza et al. (1978) concluded that hexabromobenzene had a greater effect postnatally when transmitted through the milk than when transmitted transplacentally. No treatment-related effects were noted in pups exposed prenatally, while those exposed only during lactation showed some increase in liver weights. Villeneuve and Khera (1975) reported in an abstract that the accumulation of hexabromobenzene (or its metabolites) in fetal tissue was very low, indicating only slight placental transfer.

Data on the teratogenicity of other brominated benzenes were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Mendoza et al. (1979) treated 15 female Wistar rats with 80 ppm hexabromobenzene in the diet prior to mating, during pregnancy and lactation, and after weaning for a total of 101 days. There was no apparent treatment-related effect on reproduction (the number of pups/litter or litters/mated female), fetal survival or neonatal viability.

Data on the reproductive effects of other brominated benzenes were not located in the available literature.

5.5. CHRONIC TOXICITY

The chronic toxicity of bromobenzene in rats was reported in a Russian abstract (Shamilov, 1969). Bromobenzene, administered by inhalation for 4 hours/day at 3 $\mu g/m^3$ for 140 days, produced no toxic symptoms. At a concentration of 20 $\mu g/m^3$ for the same dose schedule, bromobenzene

gradually accumulated. Toxic symptoms were decreased growth rate, decreased liver sulfur-containing compounds (probably glutathione), decreased serum proteins, reduced leukocyte, platelet and reticulocyte counts and neurological disorders.

The ability of 1,4-dibromobenzene and 1,2,4-tribromobenzene to induce microsomal enzymes was tested in male Sprague-Dawley rats (Carlson and Tardiff, 1977). Some observations relevant to toxicity were also made. Groups of rats were given (p.o.) 1,4-dibromobenzene at doses of 0, 5, 10 or 20 mg/kg/day or 1,2,4-tribromobenzene (2.5, 5 or 10 mg/kg/day) for 45 days, 90 days or 90 days plus a 30-day recovery period. No overt signs of toxicity were noted for any dose/duration group for either chemical and the only effect on body weight gain was an increase at 20 mg/kg/day of 1,4-dichlorobenzene at 45 and 90 days. Upon necropsy, rats treated with 20 mg/kg/day of 1,4-dibromobenzene for 45 or 90 days had significantly ($p<0.05$) increased liver weight/body weight. No difference was found between relative liver weights of control animals and those treated with 20 mg 1,4-dibromobenzene/kg/day for 90 days followed by a 30-day recovery period. An increase in relative liver weight was also seen in groups treated with 1,2,4-tribromobenzene at 10 mg/kg/day for 45 or 90 days; the liver was still enlarged in animals given a 30-day recovery period but a decreasing trend toward control values was noted. Lower doses of either chemical had no effect on the liver/body weight ratio. Histological examination of livers from all rats at all dose/duration levels of both compounds revealed no differences from controls (Carlson and Tardiff, 1977). No other organs were examined.

Indices of microsomal enzyme induction [increased hepatic cytochrome P-450 content, azoreductase activity and EPN (O-ethyl-O-p-nitrophenyl phenyl phosphonothioate) detoxication rate] were statistically significantly

elevated at 45 and/or 90 days of treatment at dosage levels ≥10 mg/kg/day for 1,4-dibromobenzene and ≥2.5 mg/kg/day for 1,2,4-tribromobenzene (Carlson and Tardiff, 1977). These effects were no longer seen after the 30-day recovery period.

Mendoza et al. (1977) conducted a 12-week study on the effects of hexabromobenzene on male Wistar rats fed a diet containing 0, 10, 20, 40, 80 or 160 ppm of the compound. Body weights were determined and hematological examinations were performed every 3 weeks during the experiment. At the termination of the study body weight, weight gain, hematological parameters and organ weights (liver, kidney, lungs, spleen, brain, heart and testes) were determined for treated and control rats. No differences were reported between control and treated rats, at any dose level, for any of these parameters. The only treatment-related effects were an increase in serum carboxylesterase activity toward indophenyl acetate (noted at ≥40 ppm hexabromobenzene treatment), increased porphyrin levels (not significant) and a dose-dependent accumulation of hexabromobenzene in the adipose tissue (Section 4.2.) (Mendoza et al., 1977).

Female Wistar rats (n = 15) were treated with 80 ppm dietary hexabromobenzene prior to mating, during pregnancy and lactation, and after weaning for a total of 101 days (Mendoza et al., 1979). No overt signs of toxicity were noted. There was no statistical difference for body weight or liver weight between treated and control rats, but hepatic porphyrin levels and carboxylesterase activities were elevated as compared with controls ($p<0.01$). Reproductive and fetal effects were discussed previously.

Hexabromobenzene was administered in the diet (700 nmol/kg diet, equivalent to 200 ppm) for 70 days to female Agus-strain rats (Smith and Francis, 1980). Animals were consuming ~10-15 μmoles of hexabromobenzene/day

(5.5-8.3 mg/rat/day). Although body weights did not differ from controls, liver weight of treated rats was significantly ($p<0.025$) elevated after the treatment period. Hexabromobenzene also produced elevated liver porphyrin levels ($p<0.025$). Additional toxic effects were not reported or investigated.

Data on the chronic toxicity of other brominated benzenes were not located in the available literature.

5.6. OTHER RELEVANT INFORMATION

To investigate the cumulative effects of repeated exposure to bromobenzene rats were given 1-3 daily doses (0.25 mmole/kg) and examined for hepatic biochemical changes (Pessayre et al., 1980). With repeated exposure cytochrome P-450 concentrations progressively decreased. Glutathione levels decreased within 4 hours of each dosing but recovered within 24 hours so that no cumulative effect was noted at the dose level tested. The accumulation of reactive metabolites bound to hepatic proteins, which presumably causes the hepatocellular toxicity, progressively increases after repeated dosing.

Single i.p. doses of bromobenzene (375 mg/kg) have caused centrilobular hepatic necrosis in BALB/cJ and C57BL/J mice (Lau et al., 1980). Livers were prepared and examined histologically 24 hours after treatment with comparisons made between the two strains. Hepatocellular necrosis was most extensive in the BALB/cJ mice with 9 of 10 animals showing severe centrilobular cytopathologies. In contrast, 8 of 10 treated C57BL/J strain mice had no significant hepatocellular alterations. These different histological responses to bromobenzene were associated with metabolic differences between strains. Hepatic microsomal metabolism of bromobenzene to p-bromophenol, via the toxic 3,4-epoxide intermediate, proceeds more rapidly in BALB/cJ

mice (93.4 nmol/min/100 mg protein) compared to C57BL/J strain (47.5 nmol/min/100 mg protein). Consequently, the half-life of bromobenzene is 28 minutes and 60 minutes in the two strains, respectively, the latter presumably allowing for more complete glutathione detoxication (Lau et al., 1980).

Single i.p. doses of bromobenzene (225 or 750 mg/kg) administered to male Sprague-Dawley rats caused dose-related hepatic necrosis (Reid et al., 1971b). At the higher dose, necrosis was evident within 24 hours, with maximal acidophilic degeneration and macrophage infiltration occurring within 48 hours. The lower dose level of bromobenzene induced minimal necrosis at 24 hours, more advanced necrosis at 48 hours, and well defined necrotic lesions with fibroblastic development by 72 hours.

Exposure to bromobenzene, administered intraperitoneally, has caused renal and pulmonary necrosis, in addition to hepatic necrosis, in rats and mice. Reid (1973) reported necrosis of the proximal convoluted renal tubules in male C57BL/6J mice and male Sprague-Dawley rats treated with single i.p. doses of bromobenzene (4.85 mmole/kg to mice: 9.3 mmole/kg to rats). Of the treated mice, ~80% developed necrosis within 18-24 hours, while rats were less sensitive with 10-20% developing convoluted tubule pathologies. Bromobenzene metabolite binding to renal proteins was associated with cellular damage. The author concluded that renal necrosis was caused by a metabolite formed in the liver and transported to the kidney (Reid, 1973). Bromobenzene-induced bronchiolar necrosis was also more extensive in mice than in rats (Reid et al., 1973). In mice (i.p. injection of 4.85 mmole/kg bromobenzene) complete necrosis of the epithelium in the smaller bronchi and bronchioles was evident by 48-72 hours. Only 10-20% of the rats (treated with 9.3 mmole/kg) developed any bronchial epithelium

changes. Evidence indicates that pulmonary microsomal enzymes converted the bromobenzene to a reactive metabolite, which when bound to bronchiolar epithelial cells, elicits necrosis (Reid et al., 1973).

Roes et al. (1977), available in an abstract, reported that an LD_{85} for bromobenzene was 3150 mg/kg in mice. The LT_{50} for this dose was reported to be 23 hours.

Carlson (1978) studied the effects of 1,2,4-tribromobenzene, orally administered at 20 mg/kg/day for 14 days to male Sprague-Dawley rats. The only reported effects were increased hepatic cytochrome P-450 and NADPH-cytochrome C reductase activities. Hexabromobenzene administered at 400 mg/kg/day for 14 days did not increase hepatic enzyme activities above control levels (Carlson, 1978).

Oral administration of 0.875-7.0 g/kg/day of hexabromobenzene to mice for 30 days had no effect on body weight gain, food consumption or blood serum enzymes and no internal pathologies were noted after necropsy (Kitagawa et al., 1975).

The mechanism by which bromobenzene elicits hepatic necrosis has been investigated repeatedly since Reid et al. (1971a) reported that the causative agent is a metabolite of the parent compound. When microsomal enzymes are induced (by phenobarbital), necrosis is increased; when microsomal enzymes are inhibited (by diethylaminoethyl diphenylpropylacetate), necrosis is prevented (Reid et al., 1973). When bromobenzene is metabolized rapidly, more extensive necrosis occurs due to metabolite-protein binding and glutathione depletion (Mitchell et al., 1971; Reid and Krishna, 1973). As noted in Section 4.3. of this document, bromobenzene 3,4-epoxide is the primary toxic metabolite and glutathione is necessary to conjugate and detoxify this metabolite. The actual mechanism by which bromobenzene 3,4-epoxide causes

cellular toxicity and lethality is speculative. Thor and Orrenuis (1980) noted that the first signs of bromobenzene toxicity were primarily changes in the plasma membrane of hepatocytes. Structural changes, changes to trypan blue, succinate and potassium permeability, and inactivation of surface ion dependant ATPases were reported. Casini et al. (1982) reported that hepatocellular lethality occurred by two mechanisms. The first, which is responsible for cellular death within the first 10 hours after bromobenzene exposure (in cultured hepatocytes), is due to the peroxidation of cellular lipids (which could cause plasma membrane alterations). The second, causing cell death up to 20 hours after treatment, is due to the accumulation of metabolites bound to essential cellular proteins.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Hexabromobenzene in the water (initial concentration of 73.2 µg/ℓ was reduced to 8.76 µg/ℓ during experiment) was not lethal to juvenile Atlantic salmon, Salmo salar, during a 96-hour exposure period (Zitko and Hutzinger, 1976). Data on the acute toxicity of other brominated benzenes in aquatic organisms were not located in the available literature.

6.2. CHRONIC TOXICITY

Juvenile Atlantic salmon, S. salar, (average weight 6.77 g) were fed a diet containing 7.75 µg/g of hexabromobenzene for 40 days. No mortality occurred during this period among the 20 fish and no toxic effects were reported (Zitko and Hutzinger, 1976).

Additional data on the chronic toxicity of other brominated benzenes in aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of any brominated benzene on aquatic plants or algae were not located in the available literature.

6.4. RESIDUES

The uptake and bioconcentration of hexabromobenzene in juvenile Atlantic salmon, S. salar, was studied by Zitko and Hutzinger (1976). Hexabromobenzene was administered in the diet (7.75 µg/g food) for 40 days and in the water (73.2 µg/ℓ) for 4 days. In neither case was hexabromobenzene detected in the body tissues of exposed fish, even though the detection limit was 0.004 µg/g of tissue. Hexabromobenzene was therefore designated an accumulation coefficient of 0. Although it appears that fish do not uptake and accumulate hexabromobenzene, the authors emphasized the possibility that the compound may be converted to an undetected substance in the

fish (Zitko and Hutzinger, 1976). In a later report, Zitko (1979) suggested that low water solubility and low membrane permeability contribute to the lack of hexabromobenzene accumulation. Under laboratory conditions, Ogino et al. (1979) noted the slow rate of hexabromobenzene absorption and reported a fish to water equilibration time of 35 days.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No formally recommended or promulgated ambient or occupational exposure standards or guidelines were found for any of the brominated benzenes.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of any of the brominated benzenes were not located in the available literature.

8. RISK ASSESSMENT

Carcinogenicity testing has not been conducted on any of the brominated benzenes. Bromobenzene was only slightly genotoxic in one assay with E. coli and nonmutagenic with S. typhimurium TA1530, TA1535, TA1538, S. cerevisiae D3, and Drosophila.

No chronic studies of the toxicity of the brominated benzenes were available, but subchronic studies have been performed with bromobenzene, 1,4-dibromobenzene, 1,2,4-tribromobenzene and hexabromobenzene. An abstract from the Russian literature has reported mild toxic effects (hematologic and neurologic) in rats exposed to airborne bromobenzene at 20 $\mu g/m^3$, 4 hours/day for 140 days (Shamilov, 1969). The NOEL was 3 $\mu g/m^3$. Due to uncertainties regarding the reliability of data taken from such an abstract, it is recommended that this data not be used to derive an ADI for humans.

In a 90-day study, both increased liver/body weight ratios and hepatic microsomal enzyme induction were observed for 1,4-dibromobenzene when orally administered at 20 mg/kg/day and for 1,2,4-tribromobenzene when orally administered at 10 mg/kg/day (Carlson and Tardiff, 1977). Some induction of microsomal enzymes but no effect on relative liver weight was observed for 1,4-dibromobenzene at 10 mg/kg/day and for 1,2,4-tribromobenzene at 2.5 and 5 mg/kg/day. 1,4-Dibromobenzene had no effect on any measured parameter at a dose of 5 mg/kg/day. None of these dosages (of either chemical) had any effect upon the histological appearance of the liver and no outward signs of toxicity were apparent. The highest level of exposure that produced microsomal enzyme induction without producing a change in relative liver weight can be designated as a NOAEL. Thus, the NOAEL for 1,4-dibromobenzene is 10 mg/kg/day and for 1,2,4-tribromobenzene is 5 mg/kg/day. An ADI for 1,4-dibromobenzene of 10 $\mu g/kg/day$ or 0.7 mg/day for a 70 kg man and an ADI for

1,2,4-tribromobenzene of 5 µg/kg/day or 0.35 mg/day for a 70 kg man can be estimated from these NOAELs by division by a 1000-fold uncertainty factor. This factor represents a 10-fold for both intra- and inter-species variability to the toxicity of these chemicals, and an additional 10-fold due to the relatively short duration of the study.

Hexabromobenzene has been studied, not only for its potential effects on the liver, but also for teratogenicity and neonatal toxicity. No teratogenic effects were detected in rats when the dams were intubated with 200 mg/kg on days 6-15 of gestation (Khera and Villeneuve, 1975) or when the dams were fed the chemical at 80 ppm in the diet starting 2 weeks before mating and continuing throughout gestation (Mendoza et al., 1978). Increases in relative liver weights were observed in preweanling rats nursed by dams receiving 80 ppm hexabromobenzene in the diet, regardless of whether the pups' natural mothers had received control diet or treated diet during gestation. The increase was noted at 17 but not 21 days of age. Assuming that a rat consumes the equivalent of 5% of its body weight/day as food, an 80 ppm dietary level of hexachlorobenzene corresponds to an intake of 4 mg/kg/day. The dams that received 80 ppm hexabromobenzene in the diet had increased hepatic porphyrin levels, but no increase in absolute or relative liver weight (Mendoza et al., 1979). As reported by Smith and Francis (1980), administration of 200 ppm in the diet to female rats resulted in increased liver weights and hepatic porphyrin levels. Male rats appeared to be slightly less sensitive than were female rats in that no effects on liver (or other organ) weights were seen at any dietary level and only slight increases (not statistically significant) in hepatic porphyrin levels were observed at the higher dietary levels when the males were fed 0, 10, 20, 40, 80 or 160 ppm hexabromobenzene in the diet for 12 weeks (Mendoza et al.,

1977). Hematologic parameters were examined in the male rats and found to be unaffected. The livers were not examined histologically in any of these studies on hexabromobenzene.

An ADI could be estimated for hexabromobenzene from the NOAEL of 40 ppm in the diet determined for male rats. A concentration of 40 ppm hexabromobenzene was used to estimate an ADI since the dietary exposure only increased serum esterase activity without any adverse effects (i.e., increased liver weight). A higher concentration of 80 ppm did produce adverse effects in neonatal rats. Assuming that a rat consumes the equivalent of 5% of its body weight/day as food, the intake of hexabromobenzene corresponding to this dietary level would be 2 mg/kg/day. Applying an uncertainity factor of 1000 as described previously gives an ADI of 2 µg/kg/day, or 0.14 mg/day for a 70 kg man.

Although these ADIs for these chemicals are based on subchronic studies in which only a limited range of parameters was investigated, the investigations focused on a known target organ for this class of chemicals (i.e., the liver) and on relatively sensitive indices of exposure. In addition, for 1,4-dibromo- and 1,2,4-tribromobenzene, no histological signs of hepatotoxicity were observed at dose levels twice as high as the levels designated as NOAELs. Hence these ADIs may be sufficiently protective, or even very conservative, given that large uncertainty factors were used in the calculations. Because only limited data are available for the brominated benzenes, it is not appropriate to generalize and report an ADI for the chemical class. Further studies on the carcinogenicity and toxicity of the specific compounds are necessary.

9. REFERENCES

Billings, R.E., W.G. Stillwell and R. Caprioli. 1982. Mechanism studies on the metabolism of bromobenzene to 4-bromocatechol in isolated rat hepatocytes. Fed. Proc. 41(4): 1223.

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Atmos. Sci. Center, SRI Int., Menlo Park, CA. Contract 68-02-3452. p. 198

Brown, S.L., F.Y. Chan, J.L. Jones, et al. 1975. Research program on hazard priority ranking of manufactured chemicals: Phase II, Final Report; Chemicals 1-19, Chemicals 21-40. SRI, Menlo Park, CA. (Cited in Ware and West, 1977)

Carlson, G.P. 1978. Induction of cytochrome P-450 by halogenated benzenes. Biochem. Pharmacol. 27(3): 361-363.

Carlson, G.P. and R.G. Tardiff. 1977. Effect of 1,4-dibromobenzene and 1,2,4-tribromobenzene on xenobiotic metabolism. Toxicol. Appl. Pharmacol. 42(1): 189-196.

Casini, A., M. Giorli, R. Hyland, A. Serroni, D. Gilford and J.L. Farber. 1982. Mechanisms of cell injury in the killing of cultured hepatocytes by bromobenzene. J. Biol. Chem. 257(12): 6721-6728.

Davis, E.M., H.E. Murray, J.G. Liehr and E.L. Powers. 1981. Basic microbial degradation rates and chemical by-products of selected organic compounds. Water Res. 15(9): 1125-1127. (Cited in U.S. EPA, 1983)

DeCarlo, V.J. 1979. Studies on brominated chemicals in the environment. Ann. N.Y. Acad. Sci. 320: 678-681.

Dewalle, F.B. and E.S.K. Chian. 1978. Presence of trace organics in the Delaware River and their discharge by municipal and industrial sources. Proc. Ind. Waste Conf. 32: 908-919.

Ellis, D.D., C.M. Jone, R.A. Larson and D.J. Schaeffer. 1982. Organic constituents of mutagenic secondary effluents from wastewater treatment plants. Arch. Environ. Contam. Toxicol. 11(3): 373-382.

Ewing, B.B., E.S.K. Chian, J.C. Cook, et al. 1977. Monitoring to detect previously unrecognized pollutants in surface waters. U.S. EPA, Washington, DC. EPA-560/6-77-015. p. 75

Gibson, D.T., J.R. Koch, C.L. Schuld and R.E. Kallio. 1968. Oxidative degradation of aromatic hydrocarbons by microorganisms. II. Metabolism of halogenated aromatic hydrocarbons. Biochemistry. 7(11): 3795-3802.

Gillham, B. and L. Young. 1968. Biochemical studies of toxic agents. Isolation of premercapturic acids from the urine of animals dosed with chlorobenzene and bromobenzene. Biochem. J. 109(1): 143-147.

Griffin, W.C. 1979. Emulsions. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 8, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 916.

Grimshaw, J. and A.P. de Silva. 1981. Photochemistry and photo cyclization of aryl halides. Chem. Soc. Rev. 10(2): 181-204.

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, Inc., NY.

Hesse, S., T. Wolff and M. Mezger. 1982. Formation of irreversible protein-binding metabolites during microsomal metabolism of C^{14}-labeled bromobenzene and C^{14}-labeled bromophenol. Adv. Exper. Med. Biol. 136: 387-393.

Jollow, D.J., J.R. Mitchell, N. Zampaglione and J.R. Gillette. 1974. Bromobenzene-induced liver necrosis. Protective role of glutathione and evidence for 3,4-bromobenzene oxide as the hepatotoxic metabolite. Pharmacol. 11(3): 151-169.

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Safety. 4: 26-28.

Khera, K.S. and D.C. Villeneuve. 1975. Teratogenicity studies on halogenated benzenes (pentachloro-, pentachloronitro- and hexabromo-) in rats. Toxicology. 5: 117-122.

Kitagawa, H., T. Satoh and Y. Fukuda. 1975. Subacute toxicities of hexabromobenzene. Oyo Yakuri. 9(5): 663-673.

Konasewich, D., W. Traversy and H. Zar. 1978. Status report on organic and heavy metal contaminants in the lakes Erie, Michigan, Huron and Superior basins. Great Lake Water Qual. Board.

Koss, G., H. Doering, B. Wuerminghausen and W. Koransky. 1982. Metabolic fate of hexabromobenzene in rats. Toxicol. Lett. 14(1-2): 69-77.

Larson, E.R. 1979. Flame Retardants (Halogenated). In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed , Vol. 10, M. Grayson and D. Echroth, Ed. John Wiley and Sons, Inc., NY. p. 384

Lau, S.S. and V.G. Zannoni. 1979. Hepatic microsomal epoxidation of bromobenzene to phenols and its toxicological implication. Toxicol. Appl. Pharmacol. 50(2): 309-318.

Lau, S.S. and V.G. Zannoni. 1981a. Bromobenzene epoxidation leading to binding on macromolecular protein sites. J. Pharmacol. Exp. Ther. 219(2): 563-572.

Lau, S.S. and V.G. Zannoni. 1981b. Bromobenzene metabolism in the rabbit: Specific forms of cytochrome P450 involved in 2,3- and 3,4-epoxidation. Mol. Pharmacol. 20(1): 234-235.

Lau, S.S., G.D. Abrams and V.G. Zannoni. 1980. Metabolic activation and detoxification of bromobenzene leading to cytotoxicity. J. Pharmacol. Exp. Ther. 214(3): 703-708.

Lertratanangkoon, D., M.G. Horning and B.S. Middleditch. 1982. Bilvalent sulfur metabolites of bromobenzene. Fed. Proc. 41(5): 1572.

Mackay, D., A. Bobra, W.Y. Shiu and S.H. Yalkowsky. 1980. Relationships between aqueous solubility and octanol-water partition coefficients. Chemosphere. 9(11): 701-711.

Mendoza, C.E., H.M. Vijay, J.B. Shields and G.W. Laver. 1977. Effects of hexabromobenzene on the male rat. Toxicol. Appl. Pharmacol. 41(1): 127-130.

Mendoza, C.E., B.T. Collins, J.B. Shields and G.W. Laver. 1978. Effects of hexachlorobenzene or hexabromobenzene on body and organ weights of preweanling rats after a reciprocal transfer between the treated and control dams. J. Agric. Food Chem. 26(4): 941-945.

Mendoza, C.E., J.B. Shields and G.W. Laver. 1979. Comparison of the porphyrinogenic activity of hexabromobenzene and hexachlorobenzene in primiparous Wistar rats. Bull. Environ. Contam. Toxicol. 21(3): 258-364.

Mitchell, J.R., W.D. Reid, B. Christie, et al. 1971. Bromobenzene-induced hepatic necrosis. Species differences and protection by SKF 525-A. Res. Commun. Chem. Pathol. Pharmacol. 2(6): 877-888.

Monks, T.J., J.A. Hinson and J.R. Gillette. 1982a. Bromobenzene and para-bromophenol toxicity and covalent binding *in vivo*. Life Sci. 30(10): 841-848.

Monks, T.J., S.S. Lau, L.R. Pohl and J.R. Gillette. 1982b. The use of a stable isotope in elucidating the mechanism of formation of ortho-bromophenol (ortho-BP) from bromobenzene (BB). Fed. Proc. 41(4): 1312.

Monks, T.J., L.R. Pohl, J.R. Gillette, et al., 1982c. Stereoselective formation of bromobenzene glutathione conjugates. Chem. Biol. Interact. 41(2): 203-16.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). February, 1983: Online.

Nojima, K., T. Ikarigowa and S. Kanno. 1980. Studies of photochemistry of aromatic hydrocarbons. VI. Photochemical reaction of bromobenzene with nitrogen oxides in air. Chemosphere. 9: 421-436.

NTP (National Toxicology Program). 1983. National Toxicology Program/ Carcinogenesis Testing Program: Chemicals on Standard Protocol Management Status, January 13.

Ogino, T., T. Ishida and H. Ogata. 1979. Action mechanism of environmental pollutants in living organisms. 3. Transfer of aromatic bromo compounds and hydrocarbons into fish. Okayama-ken Kankyo Hoken Senta Nempo. 3: 201-203.

Oliver, B.G., E.G. Cosgrove and J.H. Carey. 1979. Effect of suspended sediments on the photolysis of organics in water. Environ. Sci. Technol. 13(9): 1075-1077. (Cited in U.S. EPA, 1983)

Pellizzari, E.D., M.D. Erickson and R.A. Zweidinger. 1979. Formulation of preliminary assessment of halogenated organic compounds in man and environmental media. U.S. EPA, Research Triangle Park, NC. EPA 560/13-79-006. p. 469.

Pessayre, D., J.C. Wandscheer, V. Descatoire, et al. 1980. Cumulative effects of repeated doses of compounds transformed into reactive metabolites. Biochem. Pharmacol. 29(7): 1041-1047.

Pinhey, J.T. and R.D.G. Rigby. 1969. Photoreduction of chloro- and bromo-aromatic compounds. Tetra. Lett. 16: 1267-1270.

Purcell, W.P. 1979. Benzene. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 3, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 748.

Ramel, C. and J. Magnusson. 1979. Chemical induction of nondisjunction in Drosophila. Environ. Health Perspect. 31: 59-66.

Reid, W.D. 1973. Mechanism of renal necrosis induced by bromobenzene or chlorobenzene. Exp. Mol. Pathol. 19(2): 197-214.

Reid, W.D. and G. Krishna. 1973. Centrolobular hepatic necrosis related to covalent binding of metabolites of halogenated aromatic hydrocarbons. Exp. Mol. Pathol. 18(1): 80-99.

Reid, W.D., B. Christie, G. Krishna, et al. 1971a. Bromobenzene metabolism and hepatic necrosis. Pharmacology. 6: 41-55.

Reid, W.D., B. Christie, M. Eichelbaum and G. Krishna. 1971b. 3-Methylcholanthrene blocks hepatic necrosis induced by administration of bromobenzene or carbon tetrachloride. Exp. Mol. Pathol. 15(3): 363-372.

Reid, W.D., K.F. Ilett, J.M. Glick and G. Krishna. 1973. Metabolism and binding of aromatic hydrocarbons in the lung. Relation to experimental bronchiolar necrosis. Amer. Rev. Resp. Dis. 107(4): 539-551.

Ringk, W. and E.T. Theimer. 1979. Benzyl alcohol and φ-phenetyl alcohol. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 3, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 795.

Roes, U., J.G. Dent, K.J. Netter and J.E. Gibson. 1977. Effect of polybrominated biphenyls on bromobenzene lethality in mice. J. Toxicol. Environ. Health. 3(4): 663-671.

Rosenkranz, H.S. and L.A. Poirier. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 62(4): 873-892.

Ruzo, L.O., S. Safe and O. Hutzinger. 1976. Metabolism of bromobenzenes in the rabbit. J. Agric. Food Chem. 24(2): 291-293.

Sasaki, S. 1978. The scientific aspects of the chemical substance control law in Japan. In: Aquatic Pollutants: Transformation and Biological Effects, O. Hutzinger, L.H. Von Letyoeld and B.C.J. Zoeteman, Ed. Pergamon Press, Oxford. p. 283-298.

Schwarzenbach, R.P., E. Molnar-Kubica, W. Giger and S.G. Wakeham. 1979. Distribution, residence time and fluxes of tetrachloroethylene and 1,4-dichlorobenzene in Lake Zurich, Switzerland. Environ. Sci. Technol. 13(11): 1367-1373. (Cited in U.S. EPA, 1983)

Shamilov, T.A. 1969. Toxicity characteristics and hazards of bromobenzene. Gig. Tr. Prof. Zabol. 13(9): 56-58. (Rus.) (Taken from Chem. Abstr. 72:35489e)

Shelat, Y.A. and K.S. Patel. 1973. Utilization of bromobenzene as a sole source of carbon by Bacillus polymyxa. Curr. Sci. 42(10): 368. (Cited in Ware and West, 1977)

Siegers, C.P. 1978. Antidotal effects of dimethyl sulfoxide against paracetamol-, bromobenzene-, and thioacetamide-induced hepatotoxicity. J. Pharm. Pharmacol. 30: 375-377.

Simmon, V.F. 1979. In vitro assays for recombinogenic activity of chemical carcinogens and related compounds with Saccharomyces cerevisiae D3. J. Natl. Cancer Inst. 62(4): 901-909.

Simmon, V.F., H.S. Rosenkranz, E. Zeiger and L.A. Poirier. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62(4): 911-918.

Simmons, P., D. Branson and R. Bailey. 1976. 1,2,4-Trichlorobenzene: Biodegradable or not? Canadian Assoc. Textile Colourists and Chemists, 1976. Int. Tech. Conf., Quebec, Canada, October 13-15. (Cited in Ware and West, 1977)

Singh, H.B., L.J. Salas, A.J. Smith and H. Shigeishi. 1981. Measurements of some potentially hazardous organic chemicals in urban atmospheres. Atmos. Environ. 15(4): 601-612. (Cited in U.S. EPA, 1983)

Sipes, I.G., P.L. Gigon and G. Krishna. 1974. Biliary excretion of metabolites of bromobenzene. Biochem. Pharmacol. 23(2): 451-455.

Smith, A.G. and J.E. Francis. 1980. Relative abilities on a molar basis of hexafluorobenzene, hexachlorobenzene and hexabromobenzene to decrease liver uroporphyrinogen decarboxylase activity and cause porphyria in female rats. Res. Commun. Chem. Pathol. Pharmacol. 28(2): 377-384.

SRI International. 1983. Directory of Chemical Producers. United States of America. SRI, Menlo Park, CA.

Stenger, V.A. 1979. Bromine Compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 4, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 257.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. Vanderkuy and H.J. Dishburger. 1980. A rapid method for first approximation of environmental parameters utilizing reverse phase high performance liquid chromatography. Unpublished paper.

Thor, J. and S. Orrenius. 1980. The mechanism of bromobenzene-induced cytotoxicity studied with isolated hepatocytes. Arch. Toxicol. 44(1-3): 31-43.

Thor, H., P. Moldeus, R. Hermanson, et al. 1978a. Metabolic activation and hepatotoxicity. Toxicity of bromobenzene in hepatocytes isolated from phenobarbital- and diethylmaleate-treated rats. Arch. Biochem. Biophys. 188(1): 122-129.

Thor, H., P. Moldeus, A. Kristoferson, et al. 1978b. Metabolic activation and hepatotoxicity. Metabolism of bromobenzene in isolated hepatocytes. Arch. Biochem. Biophys. 188(1): 114-121.

Thor, H., P. Moldeus and S. Orrenius. 1979. Metabolic activation and hepatotoxcity. Effect of cysteine, N-acetylcysteine and methionine on glutathione biosynthesis and bromobenzene toxicity in isolated rat hepatocytes. Arch. Biochem. Biophys. 192(2): L405-413.

Thor, H., S.A. Svensson, P. Hartzoll and S. Orrenius. 1982. Biotransformation of bromobenzene to reactive metabolites by isolated hepatocytes. Adv. Exp. Med. Biol. 136A (Biol. React. Intermed. 2, Chem. Mech. Biol. Eff. Pt. A) 287-299.

U.S. EPA. 1977. TSCA (Toxic Substances Control Act). Plant and Production Search System. Searched through CIS, February, 1983.

U.S. EPA. 1983a. Hazardous air pollutant health assessment document for chlorinated benzenes. Prepared by Dynamac Corp., Environ. Control Div., Rockville, MD, for the U.S. EPA, ORD, Cincinnati, OH. (Draft)

U.S. EPA. 1983b. STORET (Water Quality Control Information System). Online, March 1983.

Villeneuve, D.C. and K.S. Khera. 1975. Placental transfer of halogenated benzenes (pentachloro-, pentachloronitro-, and hexabromo-) in rats. Environ. Physiol. Biochem. 5(5): 328-331.

Ware, A. and W.L. West. 1977. Investigation of selected potential environmental contaminants: Halogenated benzenes. OTS, U.S. EPA, Washington, DC. EPA 560-277-004. p. 297.

Wataral, H., M. Tanaka and N. Suzuki. 1982. Determination of partition coefficient of halobenzenes in heptane/water and 1-octanol/water systems and comparison with the scaled particle calculation. Anal. Chem. 54: 702-705.

Weast, R.C. 1980. Chemical Rubber Company (CRC) Handbook of Chemistry and Physics, 60th ed. CRC Press, Inc., Boca Raton, FL.

Windholz, M., Ed. 1976. Merck Index. Merck and Co., Inc., Rahway, NJ.

Yalkowsky, S.H., R.J. Orr and S.C. Valvani. 1979. Solubility and partitioning: Solubility of halobenzenes in water. Ind. Eng. Chem. Fundam. 18: 351-353.

Zampaglione, N., D.J. Jollow, J.R. Mitchell, B. Stripp and J.R. Gillette. 1973. Role of detoxifying enzymes in bromobenzene-induced liver necrosis. J. Pharmacol. Exp. Ther. 187(1): 218-227.

Zitko, V. 1979. The fate of highly brominated aromatic hydrocarbons in fish. ACS Symp. Ser. 99, Pest. Xenobiotic Metab. Aquat. Org. p. 177-182.

Zitko, V. and O. Hutzinger. 1976. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. Bull. Environ. Contam. Toxicol. 16(6): 665-673.

APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Documentation of the Threshold Limit Values for Chemical Substances in Work Air. Cincinnati, OH. 94 p.

Bruin, P., G.J. Bergen and J.J. Desta, Ed. 1980. Handling Chemicals Safely, 2nd ed. Dutch Assoc. of Safety Experts, Dutch Chemical Industry Assoc., and Dutch Safety Institute, The Netherlands. 1013 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory, 2nd ed. The London Chemical Society, London. 473 p.

NTP (National Toxicology Program). 1982. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status. Report date: December 31, 1982.

Proctor, N.H. and J. P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia, PA. 533 p.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.